

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. – 68. (Cancelled)

69. (Currently Amended) A method for producing ~~[[a]]~~ spatio-temporally-controlled site-specific somatic recombinations ~~recombination~~ in a mouse, wherein one or more gene or intergenic DNA sequences of interest naturally belonging to the genome of said mouse have been recombined, comprising:

a) obtaining a ~~transgenic~~ mouse, wherein ~~targeted cells of said transgenic mouse comprises at least:~~

~~(i) — a Cre fusion protein comprising sequentially:~~

~~—— a Cre recombinase protein;~~

~~—— a hinge region of at least 15 amino acids;~~

~~—— a polypeptide comprising the ligand binding domain of the human nuclear estrogen receptor, or of a vertebrate nuclear estrogen receptor, said polypeptide exhibiting at least one mutation relative to the wild-type form of said ligand-binding domains,~~

~~said Cre fusion protein having a negligible, or even zero recombinase activity in the absence of a synthetic ligand endowed with antiestrogenic activity, and the recombinase activity being induced by low dose of the synthetic ligand;~~

~~[[i)](ii)~~ said one or more gene or intergenic DNA sequences of interest, naturally belonging to the ~~cell~~ mouse genome, ~~which~~ are flanked by one or more recognition sites for ~~said~~ [[a]] Cre recombinase

protein, and ~~which~~ are located in one or more of the chromosomes of the genome of said mouse; and cell;

(ii) a Cre fusion protein is expressed in targeted cells of said mouse, wherein said Cre fusion protein

(a) comprises sequentially:

- said Cre recombinase protein;

- a hinge region of at least 15 amino acids; and

- a polypeptide comprising the ligand-binding domain of a human nuclear estrogen receptor, or of a vertebrate nuclear estrogen receptor, said polypeptide exhibiting at least one mutation relative to the wild-type form of said ligand-binding domains; and

(b) has a negligible, or even zero recombinase activity in the absence of a synthetic ligand endowed with antiestrogenic activity, the recombinase activity being induced by low dose of the synthetic ligand;

b) administering to said ~~transgenic~~ mouse a low dose of said synthetic ligand in order to induce Cre-mediated recombination; and

c) obtaining a recombined mouse, wherein said recombined mouse has undergone a site-specific somatic recombination of said gene or intergenic DNA sequences as a result of the after induction, by said synthetic ligand, of ~~specific~~ recombination of said gene or intergenic DNA sequences by said Cre fusion protein in at least 90% of the targeted cells of said mouse, whereas less than 5% of the targeted cells of said mouse underwent recombination of said gene or intergenic DNA sequences before step b).

70. – 73. (Cancelled)

74. (Previously presented) The method of Claim 69, wherein said one or more sites of recognition specific for said Cre recombinase protein comprise the sequences Lox P.

75. (Previously Presented) The method of Claim 69, wherein said hinge region comprises all or part of the D hinge region of a nuclear estrogen receptor.

76. (Currently Amended) The method of Claim ~~75~~ 69, wherein said hinge region comprises amino acids 282 to 301 of the sequence of SEQ ID NO. 2.

77. (Currently Amended) The method of Claim 69, wherein said polypeptide chosen from the ligand-binding domain of the nuclear human estrogen receptors is the ligand-binding domain of the human nuclear estrogen receptor α and wherein ~~that~~ said ligand-binding domain exhibits at least the following mutations:

- mutation (G400V) glycine to valine at position 400 of the sequence SEQ ID No. 2; and
- mutation (methionine-leucine) to (alanine-alanine) situated at position 543-544 (M543A/L544A mutation) of the sequence SEQ ID No. 2.

78. (Currently Amended) The method of Claim 69, wherein said Cre fusion protein is encoded by a fusion gene integrated into one or more of the chromosomes of ~~said cell of~~ said mouse, said fusion gene being under the control of expression elements ensuring its expression in the targeted cells of said mouse.

79. (Previously Presented) The method of Claim 78, wherein said expression elements are chosen from elements controlling tissue-specific and cell-specific expression or ubiquitous expression.

80. (Previously Presented) The method of claim 78, wherein said expression elements controlling expression are chosen from elements controlling expression ensuring constitutive expression or elements controlling expression ensuring inducible expression.

81. (Previously Presented) The method of Claim 78, wherein said expression element is chosen from the group composed of the promoter regions of cytokeratin 14 (K 14), of cytokeratin 5 (K 5), and of the adipocyte fatty acid binding protein 2 (aP2).

82. (Currently Amended) The method of Claim ~~78~~ 69, wherein said fusion gene having the sequence SEQ ID No. 5 encodes the fusion protein Cre-ER^{T2} having the sequence SEQ ID No. 6.

83. (Previously Presented) The method of Claim 69, wherein said DNA sequence of interest is a gene comprising RXR α .

84. (Currently amended) The method of Claim 69, wherein **the genome targeted cells** of said mouse **comprises comprise**:

- a fusion gene encoding the fusion protein Cre-ER^{T2} having the sequence ID No. 6, said fusion gene being **selectively expressed in adipocytes** under the control of the adipocyte fatty acid binding protein 2 (aP2) promoter region; **and**
- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked (“floxed”) on each side by a one lox site, the two lox sites being oriented as a direct repeat.

85. (Previously Presented) The method of Claim 69, wherein the synthetic ligand endowed with antiestrogenic activity is selected from the group consisting of Tamoxifen, 4-hydroxyTamoxifen, ICI 164 384 and ICI 182 780.

86. (Previously Presented) The method of Claim 85, wherein the synthetic ligand endowed with antiestrogenic activity is Tamoxifen or 4-hydroxyTamoxifen.